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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,725	11/30/2001	Wely B. Floriano	06618-607002	4307

20985 7590 11/29/2005

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EXAMINER	
WHALEY, PABLO S	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,725	FLORIANO ET AL.	
	Examiner	Art Unit	
	Pablo Whaley	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-16,29,31 and 36-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-16,29,31, 36-41, and 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3 pages, 6/04/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

REQUEST FOR CONTINUED EXAMINATION (RCE)

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/09/2005 has been entered.

APPLICANTS ' ARGUMENTS

Applicants' arguments, filed 04/12/2005, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

CLAIMS UNDER EXAMINATION

Claims herein under examination are claims 1-6, 8-16, 29, 31, and 36-45. Claims 1, 4, 5, 6, 31, and 36 have been amended. Claims 17-28, 30, and 32-35 have been cancelled.

CLAIM REJECTIONS - 35 USC § 112, FIRST PARAGRAPH

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

NEWLY APPLIED REJECTION

Claims 1-6, 8-16, and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1, Line 3, has been amended to recite the limitation of "providing to a computer processor structural information...of one or more ligands." This limitation has not been found in the specification. It is noted that the instant specification discloses the invention can be implemented in a computer program product "tangibly embodied in a machine-readable storage device for execution by a programmable processor" [0087]. This disclosure, however, is different from the required limitation cited in Claim 1, Line 3, because the invention as disclosed in Claim 1 has six hierarchical steps. Therefore the specification does not support the limitation of "providing to a computer processor structural information...of one or more ligands" as this is only one step in a hierarchical list of steps disclosed in Claim 1. Claims 2-6, 8-16, and 29 are rejected for being dependent from Claim 1.

CLAIM REJECTIONS - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

NEWLY APPLIED REJECTIONS

1. Claims 1-4, 8, 9, 11, 12, 16, 29, 31, 36, 37, 39, and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by DeWitte et al. (DeWitte R., Shakhnovich E., *J. Am. Chem. Soc.*, 1996, 118: 11733-11744).

DeWitte et al. disclose the use of SmoG (Small Molecule Growth), a model for ligand-protein interactions and a scoring directly related to free energy through knowledge-based potential. A large number of structures are examined by an efficient metropolis Monte Carlo molecular growth (i.e. molecular dynamic) algorithm that generates molecules through the adjoining of functional groups directly into the binding region (Abstract), as in instant Claims 1, 4, 29, and 31. The Monte Carlo growth algorithm samples the configuration space and the molecular space under the bias of knowledge-based energy, using a coarse-grained ligand design search space (p. 11735, Col. 1, Lines 17-23). For purposes of examination, the aforementioned molecular growth algorithm has been interpreted as being within the scope of "mapping of the empty volume" (as in instant Claim 36), as it "generates molecules through the adjoining of functional groups directly into the binding region" (Abstract).

Coarse-graining has included entropic effects of solvation, and the reference state has provided the effects of solvation energy and configurational entropy (p. 11735, Col. 2, paragraph 4). As with all Monte Carlo algorithms, the algorithmic temperature defines how the algorithm

responds to steps which increase the parameter being minimized (i.e. optimized) (Fig. 1, p. 11736). Thus this is a temperature dependent (i.e. annealing) molecular dynamic algorithm, as in instant Claim 1.

The model is used to score candidate structures by an evaluation (i.e. ranking) of the total binding free energy (p. 11735, Col. 2, paragraph 3). as in instant claims 1, 29, 31, and 36.

DeWitte et al. disclose preliminary selection of the lowest allowed rotamer. Atom pairs within 70% of the sum of the Van der Waals' radii are subject to energetic evaluation. The rotamer with the lowest energy is considered as a candidate for acceptance into the new molecule, as in instant Claim 8. This acceptance is determined by Monte Carlo criterion, which compares the new energy per atom with that before this growth step (p. 11736, Col. 1, paragraph 4). Results were corroborated with the enthalpic comparison performed using a well-accepted empirical force field (p. 11743, Col. 2, paragraph 2), as in instant Claim 9.

Selection of the optimal running temperature (i.e. optimization) was made by observing the distribution of energies and computation time at different temperatures (Fig. 1 and Fig. 2), as in Claims 1 and 31. The optimal algorithmic temperature generates the largest number of low energy structures per unit time.

DeWitte et al. disclose the calculation of correlations between the design energy and an estimation of binding energy using CHARMM, an empirical force field (i.e. full atom force field)(p. 11737, col. 1, paragraph 5), as in instant claims 9 and 37.

DeWitte et al. disclose a scoring method called GROW that includes empirical interaction energy and internal energy as well as surface area terms to approximate solvent effects (p. 11742, col. 2, paragraph 1), as in instant claims 11 and 39.

DeWitte et al. disclose EQUATION 1 (below) for calculating the binding energy for each ligand in the set of ligands that includes taking the difference in the ligand energy in the protein ($-T\Delta S_{complex\ formation}$) and in solution ($-T\Delta S_{solvation/desolvation}$), as in instant claims 12 and 40.

This method is able to discriminate between potential ligands that have a high probability of binding and those that do not (i.e. ranking of candidate binding energies), and is also capable of generating the favorable candidates quickly (i.e. via selection of optimal candidate binding energies) (p. 11744, Col. 1, paragraph 4). SmoG provides several advantages including simple efficient (each molecule taking just seconds on a computer), generating and evaluating whole molecules rather than separate fragments, and documented correlation between the scoring method and free energies of binding (p. 11744, Col. 2, paragraph 3), as in instant Claims 1 and 31.

DeWitte et al. disclose an example of de novo design using the protein using SmoG and CD4, an immunoglobin-family transmembrane coreceptor expressed in the helper T-cells (p. 11740, col. 1, paragraph 1), as in instant claim 16.

DeWitte et al. further disclose that by the careful choice of a contact-based interaction model, their interaction potential reflects the trends in binding free energy without free parameters, thus eliminating the need for a series of known related ligands in the hunt for a lead compound, thus enabling the use of unknown ligands (i.e. binding regions) as in instant Claim 3.

SmoG can be operated in automated, directed, or assisted modes. Automatic generation, for example, requires only the input of the protein structure (e.g. binding pocket on the CD4 protein discussed on p. 11740, Example of de novo design-CD4) and a coordinate used to specify the vicinity of the binding site, from which it proceeds to generate ligands within 5 angstroms of the specified coordinate (p. 11737, Lines 18-22), as in instant Claim 2 and 16.

Computations were carried out on a 100MHz Pentium computer running Linux (p. 11737, Line 14), which clearly discloses a computer program product as in Claims 31 and 36.

Therefore, DeWitte et al. anticipates instant claims 1-4, 8, 9, 11, 12, 13, 16, 29, 31, 36, 37, 39, and 40 of the instant application.

2. Claims 1-4, 6, 9, 11, 12, 31, 36, 37, 39, 40, 41, 43, 44 and 45 are rejected under 35 U.S.C. 102(e)(1) as being anticipated by Freire et al. (US 2001/0000807, Filed: Dec. 13, 2000; Priority Date: Jun. 2, 1998).

Freire et al. disclose a computer-based method for the identification of binding targets in proteins and other macromolecules, which includes an algorithm aimed at predicting binding targets in proteins. This algorithm allows: 1) identification of binding targets in proteins; 2) identification of additional targets if the primary target is known; 3) design of ligand molecules with optimal binding affinities for the selected target; and 4) refinement of lead compounds by defining the location and nature of chemical groups for optimal binding affinity (Abstract). More specifically, Freire et al. disclose the following aspects of their invention that are within the scope of the instant claims:

- A computer-assisted method for generating predicted binding targets of a selected molecule, using a programmed computer including a processor, an input device, and an output device, including the steps of:
- (a) inputting into the programmed computer, through the input device, data including the identity and three-dimensional coordinates of each of the atoms in the selected molecule, as in instant Claim 1 and 31.
- (b) determining, using the processor, for each atom in the selected molecule, a predicted Gibbs free energy of binding of the atom to an ideal ligand for the atom, as in instant Claims 1 and 31.
- (c) generating, using the processor, a three-dimensional prediction model of binding targets (i.e. generation of binding conformations) in the selected molecule by generating, using the three-

dimensional coordinates of each of the atoms in the selected molecule, a model of the atoms in the selected molecule and mapping onto each atom depicted in the model the corresponding determined predicted Gibbs free energy of binding, as in instant Claim 4 and 36.

- (d) outputting, to the output device, the generated three-dimensional prediction model of binding targets, as in instant Claim 1.

The invention features optimization of the conformation of ligands [Section 013] based on different degrees of solvation that define the Gibbs free energy function [Section 188], as in instant Claim 1 and 31. The algorithm employs structure-based thermodynamic analysis (Fig. 5) (i.e. annealing molecular dynamic), as in instant claim 1 and 31.

Binding targets can be known (i.e. based on experimental data) or unknown (Fig. 2), as in instant claims 2 and 3.

Lead ligands are identified either from experimental data or through ab initio calculations, i.e., calculation of an "idealized lead ligand" (FIG. 4 and FIG. 6), as in instant claim 1 and 31. Coarse-grained sorting based on binding site characteristics is disclosed (Fig. 4), as in instant claims 1 and 31. Lead ligands are modified (i.e. optimized) and the expected binding constant is calculated using the structural parameterization (FIG. 5 and FIG. 7). The binding potential (i.e. binding energy) is calculated from structure-based thermodynamic considerations [071].

Reference FIG. 11 shows the predicted and experimental binding affinities for protease/inhibitor complexes for which the structure of the free enzyme is available. Calculations based on a difference in Gibbs energies were performed by using both the structure of the free enzyme (i.e. in solution) and the structure of the enzyme in the complex but without the inhibitor (i.e. unligated) [171], as in instant claims 12 and 40.

Reference Table 1 shows the structure/solvation terms and their contributions to the total Gibbs energy of binding and, more specifically, contributions arising from the transferring of the

charge from water to an environment with a somewhat lower dielectric constant, as in instant claims 13 and 41.

In reference claim 4, Freire et al. disclose a computer-assisted method for ranking each ligand in a set of selected ligands by its predicted binding affinities (i.e. energy scoring) for binding to a selected binding site of a selected molecule, using a programmed computer including a processor, an input device, and an output device, as in instant claims 1 and 31.

Freire et al. teach the calculation of binding potential which accounts for surface areas becoming buried from the solvent upon binding, expressed as changes in solvent accessibilities, whereby their magnitude depends on the topological configuration (i.e. conformation) of the binding site [075], as in instant claims 6 and 45.

Freire et al. teach inhibitor and protease residues located in the binding pocket bury a significant non-polar surface from the solvent (i.e. within the protein), and calculate the average fraction of non-polar area buried from the solvent upon binding, and compare this value to a predetermined threshold derived from a typical globular protein upon folding [172], as in instant claims 6 and 45.

Freire et al. teach that binding energies (calculated by the aforementioned method) are proportional to the change in solvent accessibility (i.e., the amount of surface area that becomes buried from the solvent upon binding) [076], thus disclosing a surface-area based solvation model as in instant claims 11 and 39.

Freire et al. calculate the atomic accessibility (i.e. binding energy) of a free protein by subtracting the free form of the ligand from the ligand-protein complex [075], as in instant claims 12 and 40.

Freire et al. teach the selection of best binding site candidates (i.e. optimization) using the aforementioned method which incorporates a systematic search with the full atomic structures of the peptides (i.e. full atom force field) [102], as in instant claims 9 and 37.

Freire et al. generate conformations by varying the dihedral angles, identify conformations that are close to an energy minimum, use search algorithms aimed at identifying the minima of functions used, check van der Waals conditions using the set of effective van der Waals radii and reject conformations that exhibit van der Waals collisions (i.e. atomic trajectory computation, i.e. full atom force fields; see www.ks.uiuc.edu/Research/namd/2.5/ug/node6.html), and calculate Gibbs energy functions only for allowed conformations (i.e. best conformations) [117], as in instant claim 4, 6, 9, 37, and 45.

The binding site identification process, measured 3-D coordinates of a selected target molecule are input into a computer system (i.e. mapping of an empty volume available for ligand binding) (Fig. 2), as in instant claims 4 and 36.

For each atom of the target molecule, the computer processor determines a predicted Gibbs free energy of binding of the atom to the ideal ligand for that atom. A 3-D model of binding targets in the selected target molecule is then generated by the processor using the three-dimensional coordinates of each of the atoms in the selected target molecule. The corresponding predicted Gibbs free energy of binding is then mapped onto each atom depicted in the three-dimensional model of the target molecule (Fig. 2, STEP 2200). The processor identifies regions with the highest binding potential (Fig. 2, STEP 2300 and STEP 2400) and classifies each potential binding site according to chemical nature, surface area, location, etc (Fig. 2, STEP 2500). The processor selects a potential target binding site according to user criteria (e.g., type of ligand, binding affinity, size, geometry), and a three-dimensional prediction

model of the binding target is output to a suitable output device (Fig. 2, STEP 2600). Thus, Freire et al. clearly anticipates instant claims 4 and 36.

Therefore Freire et al. clearly anticipate the instant claims 1-4, 6, 9, 11, 12, 31, 36, 37, 39, 40, 41, 43, 44 and 45 of the instantly claimed invention.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

NEWLY APPLIED REJECTION

Claims 1-6, 8-12, 15, 16, 29, 31, 36-40, and 43-45 are rejected under the first paragraph of 35 USC § 103(a) as being unpatentable over Zuo et al. (1998), in further view of DeWitte et al. (DeWitte R., Shakhnovich E., *J. Am. Chem. Soc.*, 1996, 118: 11733-11744).

As stated in the previous office action, Zou et al. discloses a method and computer program for modeling ligand receptor binding interactions wherein structural information based

on solvation effects for said receptors are derived from crystal structures to identify binding regions (page 8037, columns 1-2, III. Results, § 1). Zou et al. discloses "we first use DOCK to identify 10,000 top force field scoring molecules from the ACD and then carry out the GB calculations to rank these candidates. . .We also tested the capability our free energy scoring function to select the right conformations of a binding ligand out of a variety of possible conformations " (page 8037, column 2, Rank Ordering of Binding Affinities). A 10 best scoring results (output) according to free energy calculations for a plurality of conformations are discloses in Table 4. The binding energy calculations are optimized in ordered to rank inhibitors correctly (page 8037, column 1, § 6. Optimization for the Parameter Set), as in instant claims 1, 29, 31, and 36.

The crystal structures used for identifying binding regions are derived from dhfr-MTX (page 8037, columns 2, lines 3-5), as in instant claim 2. The step of optimization for the parameter set is directed to known and unknown binding regions for predicting binding energies (page 8037, column 1, § 6. Optimization for the Parameter Set), as in instant claim 3.

Zou et al. disclose the treatment of solvent molecules in molecular dynamics simulations (page 8033, column 2, lines 14-15), where unoccupied embedded space between ligand and the receptor (empty volume) is penalized in the said method (Abstract etc.), and energy minimization performed with DOCK force field scoring (i.e. full atom force field), as in instant claims 9 and 37.

Zou et al. teach the scoring of ligand molecules based on the grid spacing of 0.3 A (first energy function) and distance cutoff of 10A (second energy function), where orientation (i.e. conformation) minimization is performed and the results are given in Table 1 (page 8037, column 2, lines 1-19 and Table 1), as in instant claims 4-6, and 8.

Zou et al. discloses a simple solvation model that uses atom or group-based solvent exposed area terms (i.e. surface-area based solvation model); and an approach wherein the solvent is treated as a continuum dielectric medium (page 8034, column 1, lines 12-13), as in instant claims 10, 11, 38, and 39. Furthermore, Zuo et al. disclose EQUATIONS 3, 4, and 6, which clearly incorporates surface area into their model, as in instant claims 11 and 39.

Zuo et al. discloses EQUATION 8 for calculating binding energy for each ligand where the binding energies are represented as the difference G_{LR} - G_L- G_R in solvent (where L= ligand, R=receptor/protein), as in instant claims 12 and 14. Zuo et al. further teach that the binding energy for each ligand is calculated by taking the difference in the ligand energy of ligand in solvent and in receptor (page 8035, columns 2, §3 and §4 to page 8036, column 1), as in instant claims 12 and 40.

Zou et al. disclose methods directed to globular protein and the calculation of dielectric constant of said protein in water (page 8035, column 1, lines 3-12), as in instant claim 16.

The method of Zou et al. above is relies on the general GB/SA model to compute ligand binding energies wherein the parameters are approximated by a linear dependence on the solvent-accessible surface area and dielectric properties around the binding site as directed to the unoccupied embedded space (page 8034, 11. Method §, column 2, to page 8035, column 1, line 26). Using the method of Zou et al., the first set of parameters yields the best fit binding energies six inhibitors (subset). TMP and MTX rank no. 1 and no. 2 among top scoring 10,000 ACD molecules for dhfr (page 8040, column 1, lines 10-19, as in instant claims 44 and 45.

Zuo et al., however, do not disclose the limitation of "preferred binding conformations being generating a set of configurations for each ligand by applying a coarse-grained docking algorithm" (Instant Claim 1). Zuo et al. instead use the bound dhfr-MTX crystal structures and bound benzamidine-tyrpsin crystal structures to acquire free energy data (Appendix 4) using

DOCK, a geometric method where the Connolly surface of the receptor is mapped onto a negative image used as the search target for similarity with molecules in a library. DOCK is limited by the extent of the library of potential candidates. The ideal computational tool for structure-based drug design is able to test *many* structures in a short period of time and arrange them into a ranked list based on an accurate prediction of binding free energies (DeWitte et al., Introduction, p.11733). This motivates the use of an algorithm for generating a larger library (i.e. set of configurations) of potential candidate ligands.

DeWitte et al. disclose the use of SmoG (Small Molecule Growth), a structure-based drug design method where a large number of structures are examined by an efficient metropolis Monte Carlo molecular growth algorithm that generates molecules through the adjoining of functional groups directly into the binding region (Abstract). This Monte Carlo growth algorithm is a search procedure that samples the configuration space and the molecular space under the bias of knowledge-based energy, using a coarse-grained ligand design search space (p. 11735, Col. 1, Lines 17-23). SmoG can be operated in automated, directed, or assisted modes. Automatic generation, for example, requires only the input of the protein structure (e.g. dhFx-MTX crystal) and a coordinate used to specify the vicinity of the binding site, from which it proceeds to generate ligands within 5 angstroms of the specified coordinate (p. 11737, Lines 18-22). DeWitte et al. further disclose that this model can also be used for scoring (i.e. ranking) candidate structures by an evaluation of the total binding energy (p.11735, Col. 2, paragraph 4).

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the invention of Zuo et al. with the additional steps of DeWitte et al., resulting in the practice of instant claims 1-6, 8-12, 15, 16, 29, 31, 36-40, and 43-45 of the instant claimed invention with a reasonable expectation of success.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571)272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ardin H. Marschel 11/15/05

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ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER